[first] enzyme moiety of the [first] bispecific reagent from the insoluble moiety, the solubilizing effect of the soluble moiety being thereby [dissipated] reduced and the remaining material being [adapted] available to form the [first] extra-cellular precipitate.

83. (amended) A [first] therapeutic agent in accordance with claim 69 which is radio-labeled.

84. (amended) A bispecific reagent which [is adapted to] can be received and bound at [a first] an antigenic receptor which is a non-endocytosing receptor of a first target cancer cell, the bispecific reagent being comprised of two moieties, the first moiety being a non-mammalian enzyme which is a first enzyme moiety [and being adapted to] which can convert a [first] therapeutic agent into an insoluble non-digestible precipitate which is [a first] an extra-cellular precipitate, the [first] bispecific reagent further [having] containing a second moiety which is a targeting agent moiety [adapted to have] which has a substantial affinity for the antigenic receptor of the [first] target cancer cell.

REMARKS

Reconsideration and allowance are respectfully requested.

The requirement of restriction has been made FINAL and therefore Claims 1-68 and 84-87 have been withdrawn from consideration under 37 CFR §1.142(b) as being drawn to claims to non-elected inventions. Consequently claims 69-83 are currently under prosecution.

Specification

In section 3. of the Action, a separate section including a description of each drawing is required. In response, it submitted that the originally filed application on

pages 14-16 contained a proper heading and description of each of the drawings of FIGS. 1-44.

Arrangement of Specification

In the subject Amendment, in response to section 3. of the Action, appropriate amendments have been made to the headings of the specification.

Claims

In view of the objection to the word "adapted" in section 5. of the Action, claims 69, 74, 75, 76, and 84 have been amended herein to replace the word "adapted".

1. Action - Section 5.(a):

> "(a) The specification gives no guidance on or exemplification, either *in vitro* or *in vivo*, of making/using a first therapeutic agent being a soluble precipitable material which is adapted to be converted into an insoluble and non-digestible precipitate by the action of a non-mammalian enzyme wherein the first therapeutic agent is selected from the group consisting of peptides, including opio-melanins, or carbohydrates including cellulose, chitosan and chitin, of proteglycans of synthetic polymers and of indoxyl compounds."

Response:

The making of soluble precipitable material is disclosed in the specification at pages 20-23 and the making of soluble precipitable material comprised of soluble and insoluble moieties is disclosed in the specification, at pages 23 and 24.

2. Action - Section 5.(a):

The specification contemplates the use of the therapeutic agent *in vivo* in the treatment of cancer (see page 2, paragraph 1 of the specification). However, the specification does not provide teachings to establish effective dosages or methods of administration of any of the claimed "adapted" moieties...".

Response:

The effective dosage and the methods of administration can be the same as the prior art described as "Antibody Dependent Enzyme Pro-Drug Therapy" ("ADEPT") on pages 9 and 10 of the specifications.

3. Action - Section 5. (a):

"...this specification does not providing teaching to... provide any guidance or exemplification on how to "adapt" any of the claimed moieties..."

Response:

The soluble precipitable material is deliberately made so that it is soluble and will precipitate by the action of an enzyme as set forth on pages 20-24 of this specification is the same as the prior art to the extent that, in ADEPT, the enzyme converts a molecule from one form into another form, but this conversion in ADEPT is that of converting a soluble pro-drug into a soluble drug. In contradistinction, in the present invention, the enzyme converts a chemical from one form to another, i.e. converts a soluble molecule into an insoluble molecule.

4. Action - Section 5.(a):

"...for any of the limitations disclosed above or provide pharmacokinetic data that would provide guidance to one of skill in the art to predict the efficacy of the claimed therapeutic agent with a reasonable expectation of success..."

Response:

The effective dosage and the method of administration can be the same as the prior art described as "Antibody Dependent Enzyme Pro-Drug Therapy" ("ADEPT") on pages 9 and 10 of the specification.

5. Action - Section 5.(a):

"Clearly, the therapeutic agents may be inactivated *in vivo* before producing a therapeutic effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life. In addition, the therapeutic agent may not otherwise reach the target because it may be absorbed by fluids, cells and tissues where the therapeutic agent has no effect, circulation into the target area may be insufficient to carry the therapeutic agent and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled inthe art and no evidence has been provided which would allow one of skill int he art to predict the efficacy of the claimed therapeutic agent with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success."

Response:

The bispecific reagent is pharmacologically inactive. It has only two functions. It can bind to the platform and it has a non-mammalian enzyme moiety which can only act on the soluble precipitable material to convert it into an insoluble material. It is irrelevant if some is degraded, if some activates an immune response, if only a small fraction reaches the target platform, and if only a small concentration is achieved. That which does reach the platform remains bound and the amount which binds continues to increase until the binding sites on the platform are saturated. The binding of the bispecific reagent is directly analogous to the binding of a bispecific reagent to cell receptors as in ADEPT which is described in pages 9 and 10 of the specification. Since the enzyme in ADEPT can convert a pro-drug into an active drug and since the soluble precipitable material has been specifically made to be soluble and convertible to an insoluble material which remains near where it was made, the claimed therapeutic efficacy will be much better than the efficacy of ADEPT where the active drug diffuses away from its site of production to reach and cause systemic toxicity (see page 24 of the specification). The reasons why ADEPT fails is described on page 10 of the specifications.

6. Action - Section 5.(a):

> "Further, the specification provides no description of how to "adapt" any of the moieties so that they will be converted into an insoluble and non-digestible precipitate by the action of a non-mammalian enzyme. Applicant has not shown that, for example, peptides which are "adapted" are capable of functioning as that which is being disclosed. It is pointed out hat the term "adapted" could be read to encompass a variety of definitions, i.e. chemical modification, deletions, truncations, substitutions, conjugation, etc. Applicant has not enabled all of these types of modified peptides.

Response:

The word "adapted" has been replaced in claims 69, 74, 75, 76, and 84.

The effective dosage and the methods of administration can be the same as the prior art described as "Antibody Dependent Enzyme Pro-drug Therapy" ("ADEPT") on pages 9 and 10 of the specification.

The soluble precipitable material is deliberately made so that it is soluble and will precipitate by the action of an enzyme as set forth on pages 20-24 of the specification is the same as the prior art described as ADEPT on pages 9 and 10 of the specification.

7. **Action - Section 5.(a):**

Protein chemistry, which reads on peptide chemistry, is probably one of the most unpredictable areas of biotechnology. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Similarly it has been shown that a glycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of a protein.

Response:

The Action is referring to the soluble precipitable material as being a protein or peptide. Proteins are <u>not</u> being claimed and the specification does <u>not</u> describe proteins and peptides as candidates for the soluble precipitable material.

8. **Action - Section 5.(a):**

"Further, Applicant has not enabled "adaptations" of all carbohydrates, proteoglycans, synthetic polymers or indoxyl compounds as claimed. Nor has Applicant given guidance on how to choose those agents that will, upon "adaptation", function as claimed."

Response:

The making of soluble precipitable material is disclosed in the specification at pages 20-23 and the making of soluble precipitable material comprised of soluble and insoluble moieties is disclosed in the specification at pages 23 and 24.

9. **Action - Section 5.(a):**

Finally it is not clear from the teaching of the specification that the insoluble, non-digestible and presumably therapeutic precipitate, resulting from the action of the bispecific reagent upon the therapeutic reagent, will remain in the extra-cellular fluid adjacent to the first bispecific reagent, and thus it is not clear that for example, if toxic, the precipitate will not exert its toxic affects on tissues and organs other than those of the first target cancer cells and therefore damage the unprotected host organism.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the

disclosure how to make/use a therapeutic agent as claimed. Therefore, undue experimentation would be required to enable the claims.

Response:

The active drug produced in ADEPT is soluble and does diffuse into the systemic circulation to cause systemic toxicity which is one reason ADEPT fails (see specification at page 10). The insoluble precipitate produced by the present invention does not diffuse away (only soluble materials diffuse) and does not move away by convection into the lymphatics because tumor tissue lacks an effective lymphatic drainage (see pages 33 and 36 of specification) and if necessary the precipitate is "tethered" to various structures (see pages 36-41 of the specification).

10. Action - Section 5.(b):

"The specification gives no guidance on or exemplification, either *in vitro* or *in vivo*, of making/using a bispecific reagent which will convert a first therapeutic agent into an insoluble and non-digestible precipitate at the site of the first target cancer cells. The claims are drawn to a targeting agent moiety and a first enzyme moiety, which is a non-mammalian enzyme moiety, which has a substantial affinity for the first antiagent receptor of the first target cancer cells and thus, as broadly written, read on bispecific antibodies with an antigen binding region and a non-mammalian enzyme region for the conversion of a pro-drug to a drug used for the treatment of cancer *in vivo*.

Response:

The bispecific reagent can be made by several published methods. The methods are now so standard and well known that no reference is made to them in the specification. The enzyme component of the bispecific reagent is chosen together with the soluble precipitable material so the enzyme does convert the soluble precipitable material from a soluble molecule into an insoluble precipitate. For example, penicillinase acts on lactams (penicillin) at position 3 of the indoxyls and when the penicillin is degraded by the enzyme, the indoxyl precipitates.

11. Action - Section 5.(b):

"The record contains insufficient evidence to establish that the claimed product is useful for treating human cancers. It is well known in the art at the time the invention was made that although antibodies were highly effective as a means of selectively targeting cancer cells, antibody based targeting of therapeutics has proved relatively ineffective in the treatment of

solid tumors such as carcinomas. WO 93/17715 specifically teaches that (1) solid tumors are generally impermeable to antibody-sized molecules; (2) that antibodies that enter the tumor mass do not distribute evenly because of the dense packing of tumor cells; and (3) antigen-deficient mutants can escape being killed by the antibody-based therapies and regrow (p. 4, lines 10-37), thus the ability to use the claimed bispecific reagent would be highly unpredictable."

Response:

The present invention was specifically made to circumvent the problems described in the Action quoted above. The first two problems, tumors impermeable to antibodies and lack of uniform distribution of the antibodies, are relevant to ADEPT, referred to above, which only partially circumvents these problems. The present invention completely circumvents these two problems because it does not matter how slowly the bispecific reagent penetrates into the tumor. The problem of antigenic deficient mutants is circumvented to some extent by ADEPT (see page 10 of the specification); however the problem is even more effectively circumvented by the present invention because the process simulates the successful treatment of thyroid cancer and creates intense radiation fields which kill all cells in each microregion including antigen deficient mutants (see pages 7, 11, and 33-34 of the specification).

12. Action - Section 5.(b):

"Further, the specification does not provide teachings to establish effective dosages or methods of administration of any of the claimed bispecific reagents. In addition, the bispecific reagent may be inactivated *in vivo* before producing a therapeutic effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life of the protein. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to ne skilled inthe art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed therapeutic agent with a reasonable expectation of success."

Response:

The dosage method of administration, and the inactivation of the bispecific reagents are the same as in ADEPT which has circumvented the problems (see pages 9 and 10 of the specification). One skilled in the art who knows ADEPT would readily recognize the increase efficacy of the present invention over ADEPT.

13. **Action - Section 5.(b):**

In addition, Applicant claims (claim 76) a first therapeutic agent selected from the group including indoxyl-lactam which is cleavable by the first enzyme moiety of the first bispecific reagent. Thus, it appears that the action of the non-mammalian enzyme on the first therapeutic agent is to render it nontherapeutic and, clearly, undue experimentation would be required to enable the claims.

Response:

Loss of antibacterial activity by the action of lactamase is certain to develop; however, with respect to the present invention, this loss is irrelevant, or more correctly, is actually required to convert a soluble indoxyl lactam into an insoluble indigoid material.

14. **Action - Section 5.(b):**

"The specification gives no guidance on or exemplification, either *in vitro* or *in vivo*, of making/using a therapeutic agent in which a cell-impermeant chemical is attached to the first therapeutic agent, the cell-impermeant chemical causing the first therapeutic agent to be cell impermeant (claim 71). The record contains insufficient evidence to establish that the claimed product is useful for treating human cancers."

Response:

Making the soluble precipitable material into a cell impermeant molecule is described at pages 19, 22, and 29-30 of the specification.

15. **Action - Section 5.(b):**

The specification gives no guidance on or exemplification of how to choose the agent to be attached to the broadly claimed first therapeutic agent or how or where to attach it.

Response:

Making the soluble precipitable material into a cell impermeable molecule is disclosed on pages 19, 22, and 29-30 of the specification.

16. Action - Section 5.(d):

The specification gives no guidance on or exemplification, either

in vitro or *in vivo*, of making/using a therapeutic agent in which a cell-impermeant chemical is attached to the first therapeutic agent to be cell impermeant wherein the cell impermeant chemical is selected from the group including materials having molecular weight greater than 1000 daltons (claim 72). Clearly, as broadly written, the claim reads on any chemical that is greater than 1000 daltons and just as clearly, the specification has not taught how to make or use any therapeutic reagent conjugated to any chemical of unlimited molecular weight.

Response:

Making the soluble precipitable material into a cell impermeable molecule is disclosed on pages 19, 22, and 29-30 of the specification. The recitation of materials having a molecular weight of greater than 1000 dollars defines a large molecule and thereby a cell impermeant chemical.

17. Action - Section 6.(a):

"Claims 69-83 are indefinite in the recitation of the phrase "having a first antigenic receptor". The claims are indefinite because it is not clear which of the heterogeneous population of cancer cells "has" a first antigenic receptor."

Response:

Claim 69 has been amended to recite that "...the target cancer cells <u>each</u> having a first <u>population</u> antigenic receptor..." The specification makes the claims 69-83 definite by reciting at page 17 that "the first sub-population of cancer cells being the first target cells 100 each having the first antigenic receptor 101".

18. Action - Section 6.(b):

"Claims 69-83 are indefinite because claim 69 recites the phrase "adapted to be converted". The claims are confusing because it is not clear what is meant by the term "adapted". Is the therapeutic agent conjugated to another molecule, is it reduced or oxidized?

Response:

The word "adapted" has been removed from claims 69, 74, 75, 76, and 84.

The effective dosage and the methods of administration can be the same as the prior art described as "Antibody Dependent Enzyme Pro-Drug Therapy" ("ADEPT") on pages 9 and 10 of the specifications.

The soluble precipitable material is deliberately made so that it is soluble and will precipitate by the action of an enzyme as set forth on pages 20-24 of the specification and is the same as the prior art described as ADEPT on pages 9 and 10 of the specification.

19. Action - Section 6.(c):

> "Claims 69-83 are indefinite because claim 69 recites the phrase "the first therapeutic...when administered...having a heterogeneous population of cancer cells". The claims are confusing because it is not clear whether the living host or the therapeutic agent has a heterogeneous population of cancer cells".

Response:

Claim 69 does not recite the phrase quoted above. The living host has a cancer which is composed of a heterogeneous population of cancer cells -- the therapeutic agent does not have a heterogeneous population of cancer cells.

20. Action - Section 6.(d):

> (d) Claims 69-83 are indefinite because claim 69 recites "adapted to be converted". The claims are confusing because neither claim 69, not the claims dependent on claim 69, claims that the first therapeutic agent is converted to a precipitate.

Response:

Claim 69 and claims dependent on claim 69 recite that the therapeutic agent is converted into a precipitate. Claim 69 recites: "...the therapeutic agent to be converted in the extra-cellular fluid of the living host, adjacent to the bispecific reagent, into a soluble and non-digestible precipitate..."

21. Action - Section 6.(e):

> Claims 69-83 are indefinite because it is not clear whether the first therapeutic agent is therapeutic before or after conversion to the insoluble and non-digestible precipitate or whether the therapeutic agent is neutralized or destroyed by the conversion process.

Response:

The therapeutic agent is radio-labeled. It is only therapeutic after it has been converted into an insoluble material because the therapeutic effect depends on the

radiation field which is generated by the precipitate induced immobilization of the isotope and its long term retention at the immobilized site. The therapeutic agent is not neutralized or destroyed by the conversion process.

22. Action - Section 6.(f):

Claims 69-83 are indefinite because claim 69 recites the phrase "adapted to be disposed adjacent". The claims are confusing because it is not clear (as disclosed above) what is meant by the term "adapted". Further, the claims are confusing because the term "disposed" is not defined either in the claims or the specification and therefore the metes and bounds of the patent protection claimed cannot be determined.

Response:

The word "adapted" has been removed from claims 69, 74, 75, 76, and 84.

The precipitate is formed by the catalytic action of the cell-bound non-mammalian enzyme and is retained adjacent to the non-mammalian enzyme. The radioactive isotope component of the therapeutic agent naturally disintegrates and releases its alpha, beta, or gamma particles or electromagnetic radiation.

23. Action - Section 6.(g):

Claims 69-83 are indefinite because claim 69 recites the phrases, "a first therapeutic agent", "first target cells", "first bispecific reagent", "first extra-cellular precipitate" without reciting any additional moieties.

Response:

The word "first" by amendments herein has been removed from claims 69-83.

24. Action - Section 6.(h):

Claims 69-83 are indefinite because claim 69 recites an improper Markush group. MPEP 706.03(y) provides that the materials set forth in a Markush group ordinarily must belong to a recognized physical class or chemical class or to an art-recognized class.

Response:

The citation of MPEP 706.03(y) is incorrect.

The Markush group of claim 69 includes compounds which have the common mechanism that they are alone time soluble and are converted by an enzymatic action to be insoluble.

MPEP 2173.05(h) recognizes that a Markush group is proper as in the combination of claim 69.

> "However, when the Markush group occurs in a claim reciting a process or a combination or a combination (not a single compound), it is sufficient if the members of the group are disclosed inthe specification to possess at least one property in common which is mainly responsible for their function in the claimed relationship, and it is clear from their very nature or from the prior art that all of them possess this property."

The present invention only claims soluble precipitable material as indoxyls and soluble precipitable material having a soluble and insoluble moiety. They function by a common mechanism, namely they are only therapeutic when and because they are radio-labeled and because they are converted from a soluble to an insoluble material, thus enabling the isotope to be retained in the immobilized state for a long time.

25. Action - Section 6.(i):

> Claims 69-83 are indefinite because claim 69 recites, in the improper Markush group disclosed above, the phrases "peptides, including...", "carbohydrates including...". the claims are confusing because it is not clear whether the peptides and carbohydrates claimed are limited to those recited in the claim or whether they include other moieties of the same class.

Response:

See response to Action - Section 6.(h) above.

26. Action - Section 6.(j):

> Claims 69-83 are indefinite because claim 69 recites "a first antigenic epitope [being...". Because there is no closing bracket, it is not possible to determine how much of the remainder of the claim is deleted by amendment.

Response:

The bracket in claim 69 has been deleted.

27. Action - Section 6.(k):

Claims 69-83 are indefinite because claim 69 recites the phrase "for an extended period of time". The term "extended" is a relative term and is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree of "extendedness" and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Response:

Claim 69 has been amended to recite "...at least several days..." which is an extended period of time.

28. Action - Section 6.(l):

Claim 72 is indefinite because claim 72 recites the phrase "materials having a molecular weight greater than 1000 daltons. the claim is confusing because the claimed materials are not defined either by the claim or by the specification, thus the metes and bounds of the claims cannot be determined, for example, could the materials include a breadbox?

Response:

Making the soluble precipitable material into a cell impermeable is disclosed on pages 19, 22, and 29-30 of the specification. The recitation of materials having a molecular weight of greater than 1000 daltons defines a large molecule and thereby a cell impermeant chemical.

29. Action - Section 6.(m):

Claims 74-75 are indefinite because claim 74 recites the phrase "adapted to be naturally converted". The claims are confusing because it is not clear (as disclosed above) what is meant by the term "adapted", thus the metes and bounds of patent protection requested are not defined. Further, the meaning of "naturally converted" is not clear.

Response:

Claims 74 and 75 have been amended to overcome this objection.

30. Action - Section 6.(n):

Claims 74-76 are indefinite because it is not clear at what point the intermediate has been adapted to be naturally converted.

Response:

See amendments to claims 74-76.

31. Action - Section 6.(o):

Claim 75 is indefinite because claim 75 recites the phrase "soluble...adapted to be naturally oxidized". The claims are confusing because it is not clear (as disclosed above) what is meant by the term "adapted", thus the metes and bounds of patent protection requested are not defined. Further, the meaning of "naturally oxidized" is unclear.

Response:

See amendment to Claim 75.

32. Action - Section 6(p):

Claim 76 is indefinite in the recitation of the phrase "and the like". The claimed indoxyls include indoxyls not actually disclosed (those encompassed by "and the like") and the scope of the claim is unascertainable. Further, the claim is confusing because the claim recites the phrase "adapted to be oxidized and dimerized".

Response:

See amendment to Claim 76.

33. Action - Section 6.(q):

Claim 77 is indefinite because it recites the phrase "includes a substance". The claim is confusing because it is not clear what substances would alter the characteristics of indoxyl compounds and first extra-cellular precipitates. Further, the claim is indefinite in the recitation of the phrase "alters the characteristics of". The claim is confusing because it is not clear what characteristics are being altered, for example, are the solubility, oxidizability or cleavability being altered?

Response:

See amendment to Claim 77.

34. Action - Section 6.(r):

Claims 78-80, and the claims dependent on said claims, are indefinite in the recitation of the phrase "alters the characteristics of". The claims are confusing because it is not clear what characteristics are being altered, foe example, are the solubility, oxidizability or cleavability being altered?

Response:

See amendments to Claims 78-80.

35. Action - Section 6.(s):

Claim 79 is indefinite in the recitation of the phrase "derivatives of benzyloxy". The claim is confusing because the term "derivatives" is not defined either in a claim or inthe specification.

Response:

See amendments to Claim 79.

36. Action - Section 6.(t):

Claim 82 is indefinite because it recites the phrase "solubilizing effect...dissipated". The claims are confusing because it is not clear what is meant by dissipation of the solubilizing effect.

Response:

See amendments to Claim 82.

37. Action - Section 6.(u):

Claims 69-83 because claim 69 recites the term "having" because it is not clear whether "having" is open or closed. It is suggested that this language be removed from the claim.

Response:

The claims have been amended to delete the term "having".

38. Action - Section 8:

Claims 69-83 are rejected under 35 U.S.C. § 102() as being

anticipated by WO 91/109134 (see attached abstract).

The claims are drawn to a bispecific reagent having a first enzyme moiety which is a non-mammalian enzyme moiety and a second moiety including a targeting agent which has a substantial affinity for the first target cancer cells and a therapeutic reagent adapted to be converted into an insoluble and non-digestible precipitate by the action of a non-mammalian enzyme.

Response:

The present invention comprises the conversion of a soluble precipitable material (which is not a pro-drug) into an insoluble and non-digestible precipitate by the enzyme moiety of the bispecific reagent. the insoluble precipitate remains adjacent to the bispecific reagent for an extended period of time, such as several days. Thus the precipitate does not enter the systemic body fluids.

The conversion of a soluble precipitable material into an insoluble and non-digestible precipitate is not shown or suggested by International Application Number WO 91/109134 where a soluble agent, being a soluble pro-drug, is converted into a soluble active drug which is digestible and which immediately diffuses away from the bispecific reagent to enter the systemic body fluids.

It is admitted in the Action regarding the reference of International Application Number WO 91/109134, that:

"The reference does not specifically teach that the therapeutic reagents are adapted to be converted into insoluble and non-digestible precipitates."

Therefore claims 69-83 as admitted in the Action can not be rejected under 35 U.S.C. § 102 as being anticipated by the International Application.

The claims to the present invention set forth the characteristics of the precipitate (formed from the soluble therapeutic agent) as being insoluble, non-digestible and having epitopes, one of which is a neo-antigenic epitope.

To the contrary in International Application Number WO 91/109134, the active drug (formed from the soluble pro-drug) is soluble, digestible, and does not have epitopes and does not have a neo-epitope. the active drug (formed from the pro-drug) is not radioactive and is not used to bind any other bispecific reagent.

The claims to the present invention set forth that the epitopes on the precipitate have the intended use of creating a radiation field or of binding a second bispecific reagent, the enzyme moiety of which converts a soluble

therapeutic agent into a second precipitate which is radioactive, thereby creating an intense radiation field.

Again to the contrary, in International Application Number WO 91/109134, the active drug (formed from the soluble pro-drug) has the intended use of diffusing through the extra-cellular fluid to have a pharmacological effect (not a radiation effect) on the neighboring cells.

In sum, the therapeutic agent of claims 69-83 is, thus, patentably distinct over the prior art and the product formed from the claimed therapeutic agent is, thus, patently distinct over the prior art.

It is submitted that the formal objections to claims 69-83 have been overcome by the amendments to the claim herein.

It is further submitted that claims 69-83 have been patentably distinguished herein especially in view of the admission in the Action that

> "The reference (International Application Number WO 91/09134 does not specifically teach that the therapeutic reagents are adapted to be converted into insoluble non-digestible precipitates"

as set forth in claims 69-83.

Therefore it is submitted that claims 69-83 should now be found to be in condition for allowance.

Favorable action is solicited.

Respectfully submitted,

Dated: September 18, 1998

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